121 (Amended) A test vector comprising:

(a) a segment derived from HIV from an HIV-infected patient, which segment comprises a protease-encoding nucleic acid, which nucleic acid has a mutation at codon 82 and a secondary mutation at codons selected from the group consisting of 73, 55, 48, 20, 43, 53, 90, 13, 84, 23, 33, 74, 32, 39, 60, 36, and 35, or a mutation at codon 90 and a secondary mutation at codons selected from a group consisting of 53, 95, 54, 84, 82, 46, 13, 74, 55, 85, 20, 72, 62, 66, 84, 48, 33, 73, 71, 64, 93, 23, 58, and 36; and

(b) an indicator gene, wherein the expression of the indicator gene is dependent upon the presence or absence of said mutations in the patient-derived segment.

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REMARKS

Claims 98-112, 114-117 and 121 are pending in the subject application. By this Amendment, applicants have amended claims 98, 101-107, 109, 110-112, 114, 116, 117, and 121. Accordingly, claims 98-112, 114-117, and 121 are still pending in the subject application.

A marked up version of the amended claims and specification is attached hereto as **Exhibit B**, pursuant to the requirements of 37 C.F.R. §1.121.

In view of the amendments and arguments below, applicants maintain that the Examiner's rejections have been overcome, and respectfully request that they be withdrawn.

Formalities

Priority

The Examiner stated that if applicants desired priority under 35 U.S.C. 119(e) and 35 U.S.C. 120, specific reference to the earlier filed application must be made in the instant application.

In response, applicants note that the application already specifies a claim to priority.

Drawings

The Examiner objected to the drawings alleging that a description of individual figures 3a-e, 4a-e, and 5a-e must be in paragraph form under the Brief Description of the Drawings section.

In response, applicants respectfully note that although the Examiner objected to Figures 3a-e, Figures 3d-e do not exist in the subject application. With respect to the remaining figures, applicants have amended the specification to include paragraph descriptions of Figures 3a-c, 4a-e, and 5a-e.

The Examiner also stated that Figure O was not labeled in the drawing and that Figures P and Q were not described in paragraph form under the Brief Description of the Drawings section.

In response, applicants attach hereto as **Exhibit C** a corrected Figure O with the appropriate labeling. With respect to Figures P and Q, applicants have amended the specification to include paragraph descriptions of theses Figures.

Finally, the Examiner objected to Figures 6 and 7, stating that Figures 6 and 7 were not described in paragraph form in the Brief Description of the Drawings section.

In response, applicants traverse the Examiner's objection to these figures and respectfully direct the Examiner's attention to page 33, lines 5-9, of the specification which contains paragraph descriptions of both Figures 6 and 7.

Specification

The Examiner objected to the disclosure stating that it contained an embedded hyperlink and/or other form of browser-executable code.

In response, applicants have deleted from the specification all hyperlinks and other forms of browser-executable code.

Claims

The Examiner objected to claims 107, 116, and 117 due to certain typographical errors.

In response, applicants note that these typographical errors have been corrected in the claims as amended.

Claim Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 98-112, 114-117, and 121 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner stated that the claims do not clearly state what is intended in the methods and the claims contain language lacking antecedent basis. Specifically, the Examiner stated that claims 98-112 and 114-117 were unclear because it could not be determined if the intent of the instant invention involved a two step assay or a one step assay. Moreover, the Examiner stated that the intended meaning of claims 101-107 and 110-112 was not clear.

In response, applicants have amended the claims to clearly indicate that the present invention comprises a one step assay. Moreover, claims 101-107 and 110-112, as amended, are clearly directed towards a method for assessing therapy effectiveness based on the presence of certain mutations at specific codon combinations.

The Examiner also rejected claim 121 as allegedly unclear because it could not be discerned if the mutation in codon 82 or 90 is part of the patient-derived segment. Moreover, the Examiner questioned that to which the resistance test vector is resistant. Finally, the Examiner questioned what the indicator gene indicates.

In response, applicants note that claim 121, as amended, indicates that the mutation at codon 82 or 90 is present in the patient-derived segment. Moreover, applicants' amended claim is directed towards a "test vector" and not a "resistance test vector". Finally, claim 121, as amended, clearly states that the indicator gene indicates the presence of mutations in the patient-derived segment.

The Examiner further rejected claims 100-107 and 110-112 due to an alleged lack of antecedent basis for various terms.

In response, applicants note that with the exception of the traversal set forth below covering claim 100, applicants have amended claims 101-107 and 110-112 to address the Examiner's concerns.

With respect to claim 100, applicants respectfully traverse and maintain that proper antecedent basis exists for the term "protease inhibitor." The term "protease inhibitor" is present in independent claim 98 from which dependent claim 100 depends via claim 99. Therefore, antecedent basis for this term exists.

In view of the above amendments and remarks, applicants maintain that claims 98-112, 114-117, and 121 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Claim Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 98-112 and 114-117 under 35 U.S.C. §112, first paragraph, as allegedly not enabling any person skilled in the art to make or use the invention commensurate in scope with these claims.

Specifically, the Examiner states that the specification does not provide enablement for some existent mutations at certain codons to denote an increase or decrease in drug resistance to a specific protease inhibitor or for the lack of mutations to indicate an increase in drug resistance.

In response, applicants respectfully traverse the Examiner's rejection. Applicants contend that the subject application is enabled. The language of the claims and the specification clearly allow one skilled in the art to make and use the subject invention.

Specifically, the language of the claims and specification disclose the relationship between the existence of mutations on certain combinations of codons and the correlating effect on drug susceptibility. The Examiner's attention is respectfully directed to the specification at page 173, line 7 to page 190, line 7, which is replete with data demonstrating the *decrease* in drug susceptibility associated with mutations of certain specified codons. In addition, the Examiner is respectfully directed to the specification at page 32, line 20 to page 33, line 3, which provides data demonstrating the *increase* in drug susceptibility associated with mutations of certain other specified codons. Therefore, applicants maintain that the claims and specification allow a person skilled in the art to make and use the invention.

The Examiner alleges that the specification does not describe the nature or characteristic of a codon mutation that would indicate resistance to a specific protease inhibitor. Therefore, the Examiner concludes that an undue amount of experimentation would be required of the skilled artisan to predict which drugs a patient will be resistant to based on analyzing the codon sequence.

In response, applicants respectfully traverse the Examiner's rejection. Applicants direct the Examiner's attention to the specification at page 56, line 19 to page 57, line 3, which states the specific types of mutations that lead to changes in drug susceptibility. Applicants stress that the identity of these codons is set forth in the claims, and thus, no experimentation is required to determine their identities.

Finally, the Examiner alleges that due to the ambiguity of the claims, the knowledge of the skilled artisan, and the state of

the art which indicates that certain codon mutations are associated with drug resistance, an undue amount of experimentation would be required of the skilled artisan to make or use the invention.

In support, the Examiner relies on Young et al. as allegedly demonstrating that the codon mutations which applicants maintain indicate drug susceptibility actually indicates drug resistance. Bases on this alleged teaching, the Examiner concludes that the unpredictability in the art leads to an undue amount of experimentation by the skilled artisan.

In response, applicants respectfully traverse the Examiner's rejection and maintain that the subject invention is enabled. Young et al. is inapposite to the enablement of the subject invention. That is, as previously mentioned, the language of the claims and specification disclose the precise relationship between drug susceptibility and the existence of mutations at specific combinations. Young et al. fails to teach any drug susceptibility results relating to the *specific* mutations recited in the rejected claims. Hence, applicants maintain that Young et al. has no bearing on the enablement of the claimed methods.

In view of the above remarks, applicants maintain that claims 98-112 and 114-117 satisfy the requirements of 35 U.S.C. §112, first paragraph.

Claim Rejections Under 35 U.S.C. §102(b)

The Examiner rejected claims 98-102, 104, 105, 107, 108, 110, 112, 114-116 and 117 under 35 U.S.C. §102(b), as allegedly anticipated by Young et al.

In response, applicants respectfully traverse the Examiner's rejection. For Young et al. to anticipate any of the rejected claims, it would have to teach each and every element thereof. This it fails to do. Specifically, Young et al. fails to set forth a method comprising a step of detecting in a HIV nucleic acid the presence of the specific combination of mutations recited in the rejected claims. The Examiner has failed to show otherwise. Therefore, applicants maintain Young et al. does not anticipate the rejected claims.

The Examiner also rejected claims 98-100, 107-109 and 117 under 35 U.S.C. §102(b), as allegedly anticipated by Hertogs et al.

In response, applicants respectfully traverse the Examiner's rejection. For Hertogs et al. to anticipate any of the rejected claims, it would have to teach each and every element thereof. It does not do this for the same reasons Young et al. fails to anticipate the claimed invention.

In view of the above remarks, applicants maintain that claims 98-102, 104, 105, 107, 108, 110, 112, 114-116 and 117 satisfy the requirements of 35 U.S.C. §102(b).

Claim Rejections Under 35 U.S.C. §103(a)

The Examiner rejected claim 117 under 35 U.S.C. §103(a), alleging that the claim is obvious over Young et al. or Hertogs et al.

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, the Examiner must

demonstrate three things with respect to each claim. First, the cited references, when combined, teach or suggest every element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Applicants maintain that the cited references fail to support a *prima facie* case of obviousness of claim 117.

Specifically, as set forth above and as the Examiner concedes, neither of the cited references alone teaches the specific permutations of codon mutations set forth in the rejected claims. Applicants maintain that routine skill in the art also does not provide such a teaching alone, or in combination with either cited reference. Again, the Examiner has not shown otherwise. Accordingly, neither cited reference, in combination with routine skill, teaches or suggests any element of the claims. For this reason, applicants maintain that claim 117 is not *prima facie* obvious over Young et al. or Hertogs et al.

The Examiner also rejected claim 121 under 35 U.S.C. §103(a), as allegedly unpatentable over Hertogs et al. as applied to claims 98-100 and 107-109, and further in view of Capon et al. (U.S. Patent No. 5,837,464).

In response to the Examiner's rejection, applicants respectfully traverse, and maintains that the Examiner has failed to establish a *prima facie* case of obviousness.

As stated, Hertogs et al. does not teach or suggest the combinations of codon mutations set forth in the rejected claims.

Capon et al. fails to remedy the deficiency of Hertogs et al. in that it does not identify or disclose a single codon mutation.

Therefore, the cited references, in combination, fail to teach or suggest each element of the rejected claims. For this reason, applicants maintain that claims 117 and 121 are not *prima facie* obvious over Hertogs et al. or Capon et al.

In view of the above remarks, applicants maintain that claims 117 and 121 satisfy the requirements of 35 U.S.C. §103(a).

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

COPY OF PAPERS
ORIGINALLY FILED

Applicants : Neil T. Parkin and Rainer A. Ziermann
Serial No. : 09/766,344
Filed : January 19, 2001

No fee, other than the enclosed $460.00 fee for the three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

Assistant Commissioner for Patents, Washington, D.C. 20231.

7/15/02
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Table 1: PRI susceptibility of selected patent samples. Viruses displaying increased susceptibility to amprenavir (5-fold or greater) were genotyped and found to contain the N88S mutation in PR. Samples were listed in order of decreasing susceptibility.

Table 1

Sample ID	Prior PRI Experience	SQV	Fold Change vs. Reference IDV	RTV	NFV	AMP	PR Mutations
0732	NFV	0.73	2.11	1.72	**8.92**	0.08	K14R, I15V, K20T, E35D, M36I, R41K, I62V, L63Q, N88S
627	IDV	0.26	**6.16**	1.50	**21.06**	0.09	I13I/V, E35D, M46L, L63P, I64V, I73V, N88S
1208	NFV	1.55	**3.15**	1.22	**11.06**	0.10	I62V,L63P, V77I, N88S
360	IDV	1.88	**6.31**	1.49	**29.95**	0.15	I13V, K20M, M36V, N37A, M46I, I62V, L63P, N88S, I93L
0910	NFV	1.41	**5.17**	1.85	**16.76**	0.16	M46I, L63P, V77I, N88S, I93I/L
3542	IDV	1.28	**7.61**	**3.36**	**24.67**	0.16	I13V, K14R, N37D, M46I, L63P, N88S, I93L
3654		1.80	**7.56**	1.95	**18.61**	0.20	I13V, R41K, M46I, L63P, V77I, N88S, I93L

Fold Change Limits: **>2.5** < 0.4

Table 2: PRI susceptibility of site-directed mutants in PR. Mutations were introduced into the drug sensitive reference resistance test vector and the susceptibility to PRIs were determined.

Table 2

Fold Change vs. reference

Site-Directed Mutations	SQV	IDV	RTV	NFV	AMP
L63P	1.04	1.12	1.27	1.43	1.06
L63P, V77I	1.24	1.72	1.73	2.49	0.91
N88S	0.47	1.56	0.36	2.39	0.04
L63P, N88S	1.44	**2.56**	0.77	**5.10**	0.11
L63P, V77I, N88S	1.24	**3.09**	1.39	**12.89**	0.08
M46L, L63P, N88S	1.15	2.30	0.85	**6.18**	0.12
M46L, L63P, V77I, N88S	1.45	**2.97**	1.[illegible]	**12.24**	0.14

Fold Change Limits: <0.4 **>2.5**

Applicants : Neil T. Parkin and Rainer A. Ziermann
Serial No. : 09/766,344
Filed : January 19, 2001

Exhibit B

The paragraph beginning on page 7, line 15, has been replaced with the following paragraph:

As new protease inhibitors are developed, the ability of certain amino acid substitutions to confer resistance to the inhibitor is usually determined by several methods, including selection of resistant strains in vitro, site-directed mutagenesis, and determination of amino acid changes that are selected during early phase clinical trials in infected patients. While some amino acid substitutions are specifically correlated with resistance to certain protease inhibitors (see below), there is considerable overlap between sets of mutations implicated in resistance to all approved protease inhibitors. Many investigators have attempted to classify these mutations as either being "primary" or "secondary", with varying definitions. For example, some investigators classify as primary mutations which are predicted, based on X-ray crystallographic data, to be in the enzyme active site with the potential for direct contact with the inhibitor. (e.g. D30N, G48V, I50V, V82A/F/S/T, I84V, N88S, L90M). Secondary mutations are usually considered as being compensatory for defects in enzyme activity imposed by primary mutations, or as having enhancing effects on the magnitude of resistance imparted by the primary mutations (e.g. L10I/F/R/V, K20I/M/R/T, L24I, V32I, L33F/V, M36I/L/V, M46I/L/V, I47V, I54L/V, L63X, A71T/V, G73A/S/T, V77I, N88D). Lists of either being "primary" or "secondary", with varying definitions. For example, some investigators classify as primary mutations which are predicted, based on X-ray crystallographic data, to

be in the enzyme active site with the potential for direct contact with the inhibitor. (e.g. D30N, G48V, I50V, V82A/F/S/T, I84V, N88S, L90M). Secondary mutations are usually considered as being compensatory for defects in enzyme activity imposed by primary mutations, or as having enhancing effects on the magnitude of resistance imparted by the primary mutations (e.g. L10I/F/R/V, K20I/M/R/T, L24I, V32I, L33F/V, M36I/L/V, M46I/L/V, I47V, I54L/V, L63X, A71T/V, G73A/S/T, V77I, N88D). Lists of al., Human Immunodeficiency Virus Reverse Transcriptase and Protease Sequence Database, Nucleic Acids Research 1999, 27(1), 348-352 [also accessible via the internet at http://www.viral-resistance.com/ or http://hivdp.stanford.edu/hiv/.]

The paragraph beginning on page 32, line 1, has been replaced with the following paragraph:

[Fig. 3] Figures 3a-3c

Examples of phenotypic drug susceptibility profiles. Data are analyzed by plotting the percent inhibition of luciferase activity vs. log10 concentration. This plot is used to calculate the drug concentration that is required to inhibit virus replication by 50% (IC50) or by 95% (IC95). Shifts in the inhibition curves towards higher drug concentrations are interpreted as evidence of drug resistance. Figure 3a shows the typical curve of drug susceptibility for the nucleoside reverse transcriptase inhibitor AZT. Figure 3b shows the typical curve of drug susceptibility for the non-nucleoside reverse transcriptase inhibitor efavirenz. Finally, Figure 3c shows the typical curve of drug susceptibility for the protease inhibitor indinavir. A reduction in drug

susceptibility (resistance) is reflected in a shift in the drug susceptibility curve toward higher drug concentrations (to the right) as compared to a baseline (pre-treatment) sample or a drug susceptible virus reference control, such as pNL4-3 or HXB-2, when a baseline sample is not available.

The paragraph beginning on page 32, line 20, has been replaced with the following paragraph:

[Fig 4] Figs. 4a-e
Phenotypic PRI susceptibility profile: patient 0732. A PCR-based phenotypic susceptibility assay was carried out giving the phenotypic drug susceptibility profile showing decreased susceptibility to nelfinavir and indinavir, and increased susceptibility amprenavir. Figure 4a shows a dose response relationship in subjects treated with saquinavir. Figure 4b shows a dose response relationship in subjects treated with indinavir. Figure 4c shows a dose response relationship in subjects treated with ritonavir. Figure 4d shows a dose response relationship in subjects treated with nelfinavir. Finally, Figure 4e shows a dose response relationship in subjects treated with amprenavir.

The paragraph beginning on page 32, line 27, has been replaced with the following paragraph:

[Fig 5] Figs. 5a-e
Phenotypic PRI susceptibility profile of a protease mutant generated by site-specific oligonucleotide-directed mutagenesis. A PCR-based phenotypic susceptibility assay was carried out giving the phenotypic drug susceptibility profile

of a virus having substitutions at codons 63, 77, and 88 (L63P, V77I, and N88s). The profile demonstrated resistance to both nelfinavir and indinavir, and increased susceptibility to amprenavir. Figure 5a shows a dose response relationship in subjects treated with saquinavir. Figure 5b shows a dose response relationship in subjects treated with indinavir. Figure 5c shows a dose response relationship in subjects treated with ritonavir. Figure 5d shows a dose response relationship in subjects treated with nelfinavir. Finally, Figure 5e shows a dose response relationship in subjects treated with amprenavir.

Claims 98, 101-107, 109-112, 114, 116, 117 and 121 have been amended as follows:

98 (Amended) A method of assessing the effectiveness of protease antiretroviral therapy of an HIV-infected patient comprising:

(a) collecting a biological sample from the HIV-infected patient; and

(b) evaluating whether the biological sample contains nucleic acid encoding HIV protease having a mutation at codon 82 and a secondary mutation at codons selected from the group consisting of 73, 55, 48, 20, 43, 53, 90, 13, 84, 23, 33, 74, 32, 39, 60, 36, and 35, or a mutation at codon 90 and a secondary mutation at codons selected from the group consisting of 53, 95, 54, 84, 82, 46, 13, 74, 55, 85, 20, 72, 62, 66, 84, 48, 33, 73, 71, 64, 93, 23, 58, and 36[; and determining a change in susceptibility to a protease inhibitor] ,the

presence of such protease-encoding nucleic acid in the patient's sample indicating a change in the patient's susceptibility to a protease inhibitor.

101 (Amended) The method of claim 100, [having] wherein the nucleic acid has a mutation at codon 82 and a secondary mutation at codons selected from the group consisting of 84, 48, 23, 73, 53, 33, 74, 20, 90, 32, and 39 or a mutation at codon 90 and a secondary mutation at codons selected from the group consisting of 53, 66, 84, 54, 48, 33, 73, 20, 71, 64, and 93, wherein the protease inhibitor is saquinavir.

102 (Amended) The method of claim 101, [having] wherein the nucleic acid has a mutation at codon 82 and a secondary mutation at codons selected from the group consisting of 84, 48, 23, 73, 53, 33, 74, 20, and 90, or a mutation at codon 90 and a secondary mutation at codons selected from the group consisting of 53, 66, 84, 54, 48, 33, 73, 20, and 71, wherein the change in the patient's susceptibility to a protease inhibitor is indicated by a decrease in susceptibility to saquinavir.

103 (Amended) The method of claim 101, [having] wherein the nucleic acid has a mutation at codon 82 and a secondary mutation at codons 32 or 39, or a mutation at codon 90 and a secondary mutation at codons 64 or 93, wherein the change in the patient's susceptibility to a protease inhibitor is indicated by an increase in susceptibility to saquinavir.

104 (Amended) The method of claim 100, [having] wherein the nucleic acid has a mutation at codon 90 and a secondary mutation at codons selected from the group consisting of 53, 95, 54, 84, 82, 46, 13, 74, wherein the protease inhibitor is indinavir.

105 (Amended) The method of claim 104, [having] wherein the nucleic acid has a mutation at codon 90 and a secondary mutation at codons selected from the group consisting of 53, 95, 54, 84, 82, and 46, wherein the change in the patient's susceptibility to a protease inhibitor is indicated by a decrease in susceptibility to indinavir.

106 (Amended) The method of claim 104, [having] wherein the nucleic acid has a mutation at codon 90 and a secondary mutation at codons 13 or 74, wherein the change in the patient's susceptibility to a protease inhibitor is indicated by an increase in susceptibility to indinavir.

107 (Amended) The method of claim 100, [having] wherein the nucleic acid has a mutation at codon 82 and a secondary mutation at codons selected from the group consisting of 73, 55, 48, 20, 43, 53, 90, 13, 23, 84, 53, 74, 60, 33, 36, 35, 32, and 46 or a mutation at codon 90 and a secondary mutation at codons selected from the group consisting of 95, 55, 54, 82, 85, 84, 20, 72, 62, 74, 53, 48, 23, 58, 36, 64, 77, and 93.

109 (Amended) The method of claim 108, [wherein step(c) is determining a change in] wherein the change in the patient's susceptibility to the protease inhibitor is

greater than 10 fold.

110 (Amended) The method of claim 108, wherein the nucleic acid has a mutation at codon 82 and a secondary mutation at codons selected from the group consisting of 48, 23, 84, 53, 74, 20, 60, 33, 36, 35, or a mutation at codon 90 and a secondary mutation at codons selected from the group consisting of 84, 53, 48, 23, 58, 20, 36, and 54, wherein the change in the patient's susceptibility to a protease inhibitor is indicated by a decrease in susceptibility to saquinavir.

111 (Amended) The method of claim 108, [having] <u>wherein the nucleic acid has</u> a mutation at codon 82 and a secondary mutation at codons 32 or 46, or a mutation at codon 90 and a secondary mutation at codons 64, 77, or 93, wherein the change in the patient's susceptibility to a protease inhibitor is indicated by an increase in susceptibility to saquinavir.

112 (Amended) The method of claim 108, [having] <u>wherein the nucleic acid has</u> a mutation at codon 82 and a secondary mutation at codons selected from the group consisting of 73, 55, 48, 20, 43, 53, and 90, or a mutation at codon 90 and a secondary mutation at codons selected from the group consisting of 95, 55, 54, 82, 85, 84, 20, 72, and 62, wherein the change in the patient's susceptibility to a protease inhibitor is indicated by a decrease in susceptibility to indinavir.

114 (Amended) A method of assessing the effectiveness of

protease antiretroviral therapy of an HIV-infected patient comprising:

(a) collecting a biological sample from the HIV-infected patient; and

(b) evaluating whether the biological sample contains nucleic acid encoding HIV protease having a mutation at codon 90 and secondary mutations of at lease three codons; [and (c) determining a decrease in susceptibility to saquinavir] the presence of such protease encoding nucleic acid in the patient's sample indicating a change in the patient's susceptibility to a protease inhibitor.

116 (Amended) The method of claim 114, wherein the secondary mutation [are] is selected from the group consisting of codons 10, 20, 52, 53, 54, 66, 71, 73, and 84.

117 A method of assessing the effectiveness of protease antiretroviral therapy of an HIV-infected patient comprising:

(a) collecting a biological sample from the HIV-infected patient; and

(b) evaluating whether the biological sample contains nucleic acid encoding HIV protease having a mutation at codon 82 and a secondary mutation at codons selected from the group consisting of 33, 23, 84, 32, 53, 90, 37, 71, 10, 54, 61, 11, and 46, or a mutation at codon 90 and a secondary mutation at codons selected from the group consisting of 89, 53, 84, 33, 92, 95, 54, 58, 46, 82, 36, 10, 62, 74, 15, 47, 66, 32, 55, 53, 13, and 69 [; and (c)

determining a change in susceptibility to amprenavir] , the presence of such protease-encoding nucleic acid in the patient's sample indicating a change in the patient's susceptibility to a protease inhibitor.

121 (Amended) A [resistance] test vector comprising [an] :

(a) a segment derived from HIV from an HIV-infected patient [derived segment comprising nucleic acid encoding protease having], which segment comprises a protease- encoding nucleic acid, which nucleic acid has a mutation at codon 82 and a secondary mutation at codons selected from the group consisting of 73, 55, 48, 20, 43, 53, 90, 13, 84, 23, 33, 74, 32, 39, 60, 36, and 35, or a mutation at codon 90 and a secondary mutation at codons selected from a group consisting of 53, 95, 54, 84, 82, 46, 13, 74, 55, 85, 20, 72, 62, 66, 84, 48, 33, 73, 71, 64, 93, 23, 58, and 36 [and]; and

(b) an indicator gene, wherein the expression of the indicator gene is dependent upon the presence or absence of said mutations in the patient-derived segment.

FIGURE O